

# Cannabis involvement and neuropsychological performance: findings from the Human Connectome Project

Tashia Petker, MSc; Max M. Owens, PhD; Michael T. Amlung, PhD; Assaf Oshri, PhD; Lawrence H. Sweet, PhD; James MacKillop, PhD

**Background:** There is evidence that heavy cannabis use is associated with decrements in cognitive performance, but findings are mixed and studies are often limited by small sample sizes and narrow adjustment for potential confounding variables. In a comparatively large sample, the current study examined associations between multiple indicators of cannabis use in relation to performance on a variety of neuropsychological tasks. **Methods:** Participants were 1121 adults (54% female) enrolled in the Human Connectome Project. Cannabis involvement comprised recent cannabis use (positive tetrahydrocannabinol screen), total number of lifetime uses, cannabis use disorder and age at first use. The neuropsychological battery comprised performance in episodic memory, fluid intelligence, attention, working memory, executive function, impulsive decision-making, processing speed and psychomotor dexterity. Covariates were age, sex, income, family structure and alcohol and tobacco use. **Results:** Positive urinary tetrahydrocannabinol status was associated with worse performance in episodic memory and processing speed, and positive cannabis use disorder status was associated with lower fluid intelligence (all  $p < 0.005$ ). No other significant associations were present. **Limitations:** The sample was limited to young adults aged 22–36 years. The measures of cannabis involvement were relatively coarse. **Conclusion:** Beyond an array of potential confounders, recent cannabis use was associated with deficits in memory and psychomotor performance, and cannabis use disorder was associated with lower overall cognitive functioning in a large normative sample of adults. The findings pertaining to recent use have particular relevance for occupational settings.

## Introduction

Cannabis is one of the most commonly used psychoactive drugs in the world: an estimated 2.5% of the world's population has reported cannabis use in the last year.<sup>1</sup> Increases in use are particularly apparent among adolescents and young adults,<sup>2</sup> and may escalate further with legalization of recreational use in several states in the United States and nationwide in Canada. Frequent cannabis use has been associated with a number of adverse health consequences, such as motor vehicle injuries, cannabis use disorder (CUD), increased risk of psychotic disorders and chronic bronchitis.<sup>3,4</sup>

There is also considerable concern about the adverse effects of cannabis use on cognitive abilities, such as memory, attention and learning. Of the many chemical constituents found in cannabis, the most well studied is the psychoactive component  $\Delta^9$ -tetrahydrocannabinol (THC). Acute administration of THC has been shown repeatedly to decrease performance on a variety of neuropsychological tasks.<sup>5</sup> In addition, many studies have reported associations between long-term cannabis use and impaired cognition,

both during and after acute intoxication, although the evidence to date is mixed in terms of consistent findings and methodological rigour. A recent systematic review by Broyd and colleagues<sup>5</sup> synthesized the literature examining the acute and residual effects of cannabis use on performance during task-based neuropsychological measures. Based on findings from 105 studies, they found consistent evidence for the detrimental effect of both acute and chronic cannabis use on verbal learning and memory, attention and psychomotor performance. However, the evidence for effects on other cognitive domains (i.e., working memory, executive function and decision-making) was weak, conflicting or both. Another systematic review by Ganzer and colleagues<sup>6</sup> focused on the neurocognitive effects of chronic cannabis use during an extended period of abstinence, finding evidence for persistent memory deficits during abstinence and mixed findings for other cognitive domains. Finally, although few studies have investigated the effects of cannabis use on motor learning, a recent synthesis of the existing literature identified evidence for persistent motor deficits and emphasized the need for further investigation.<sup>7</sup>

**Correspondence to:** J. MacKillop, McMaster University, 100 West 5th St., Hamilton, ON L8N 3K7; jmackill@mcmaster.ca

Submitted Jul. 23, 2018; Revised Dec. 20, 2018; Accepted Feb. 17, 2019; Published online June 27, 2019

DOI: 10.1503/jpn.180115

Across the existing literature, however, there are substantial inconsistencies in the links between cannabis and cognition. In turn, the observed inconsistency in findings has been interpreted as potentially resulting from heterogeneity in study methods, such as different or low-resolution measures and the potential impact of other substance use or other confounders that are not addressed. A further issue is statistical power: most studies have had relatively small sample sizes. This is understandable, because high-quality, comprehensive neuropsychological assessment is a time-consuming process that is not easily scaled to large cohorts, but underpowered studies may have contributed to inconsistent findings nonetheless. Small sample size is also problematic in terms of incorporating potential confounders. Because cannabis use often co-occurs with alcohol and tobacco use and has links to broader demographic variables, it is critical that these factors be considered to determine whether cannabis is specifically related to cognition, but small studies cannot incorporate an extensive number of covariates.

There is also concern about the extent to which age at first cannabis use affects cognitive performance, because people who begin using cannabis during critical periods of brain development may be vulnerable to lasting neuropsychological changes. Previous studies suggest that a younger age of initiation is associated with heavier cannabis use and more severe and enduring deficits.<sup>8–10</sup> The evidence for this association, however, comes largely from cross-sectional data, and therefore cannot speak to the causality of early use with cognitive changes. To date, only a handful of prospective longitudinal studies have explored the association between adolescent cannabis use and neuropsychological impairment, the methods and findings of which are largely mixed.<sup>11,12</sup> Thus, whether there is a link between age of first cannabis use and persistent deficits in cognition is still an open question.

Given these limitations, the current study leveraged data from the Human Connectome Project (HCP) to examine cannabis involvement and cognitive functioning. The HCP is a large-scale open-science investigation of brain connectomics in a relatively large cohort of generally healthy, normative adults aged 22–36 years.<sup>13</sup> The tasks examined in this study were selected to assess a broad array of cognitive faculties and were not restricted to domains previously identified as being affected by cannabis exposure. Thus, the advantages of the HCP data set are that it provides a large sample size, a broad cognitive scope and a sample that is generally representative of healthy young adults (as opposed to a highly selected, high-severity sample). Specifically, the study sought to parse which aspects of cannabis involvement were significantly associated with neurocognitive performance. We defined cannabis involvement using multiple indicators, including recent use (urine THC+), total lifetime use, CUD and age at first cannabis use. We assessed neurocognitive performance using an extensive neuropsychological battery that assayed a variety of neurocognitive domains. The overarching hypothesis was that greater cannabis use would be associated with poorer cognitive performance, but because of inconsistencies in the existing literature, no specific *a priori* hypotheses were specified by cognitive domain or cannabis

indicator. Finally, because some cannabis-related sex differences have been reported,<sup>14</sup> we examined sex-specific associations for exploratory purposes.

## Methods

### *Participants*

Participants made up the full sample from the Washington University–University of Minnesota Consortium HCP young adult cohort. Exclusion criteria included severe neurodevelopmental disorders, pre-existing psychiatric or neuropsychiatric disorders, other illnesses that could confound neuroimaging data (e.g., high blood pressure, diabetes), and premature birth. See Van Essen and colleagues<sup>13</sup> for a detailed description of recruitment and screening procedures. Missing data patterns are described in the statistical analysis section. All participants provided informed consent, and all aspects of the protocol were approved by the Washington University School of Medicine Institutional Review Board.

### *Assessment: substance use*

We evaluated substance use involvement with the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA).<sup>15</sup> The cannabis module included the following measures: ever used cannabis (yes/no), age at first use (grouped by age bins < 14, 15–17, 18–20, 20+, coded such that earlier age reflected greater severity), and number of times ever used cannabis (1–5, 6–10, 11–100, 101–999, 1000+). Problematic cannabis use was assessed using the SSAGA module for DSM-IV-TR marijuana abuse and/or dependence; participants who met the criteria for abuse or dependence were coded as CUD+.

The SSAGA alcohol module assessed the quantity, frequency and severity of alcohol use. The present analyses included a measure of frequency of drinking in the last year. Similarly, we assessed tobacco use with the SSAGA self-report items and included the number of days in the past 7 that participants reported any tobacco use as a measure of recent smoking status.

On the same day as the neurocognitive task assessments, participants were assessed using a breathalyzer (AlcoHAWK Pro; 100% provided a breath alcohol < 0.05) and a urine drug screen (Alere iScreen 6-panel urine drug test dip card; DOA-164-551), which assessed for the presence of THC, amphetamine, cocaine, methamphetamine, opiates and oxycodone. Recent use of cannabis was operationalized as a positive result for THC in the urine drug screen.

### *Assessment: neurocognitive tasks*

#### **Picture Sequence Memory Test**

Episodic memory was assessed using the Picture Sequence Memory Test from the NIH Toolbox.<sup>16</sup> Within a trial, illustrated objects and actions are presented 1 at a time, arranged into a demonstrated order, and then back to a random order. The participant must move the pictures into the

demonstrated order. Scores are determined based on the total number of correctly positioned adjacent pairs of pictures over 3 learning trials and converted to an age-adjusted score. Sequence lengths vary from 6 to 18 pictures, depending on the participant's age; participants in the HCP data set were presented with 15-picture sequences.

### **Raven's Progressive Matrices**

Fluid intelligence was measured using an abbreviated version of Raven's Progressive Matrices,<sup>17</sup> which has 24 items and 3 bonus items, arranged in increasing order of difficulty. The participant is presented with arrangements of squares (i.e.,  $2 \times 2$ ,  $3 \times 3$ , or  $1 \times 5$ ) forming a pattern, with 1 square missing. The participant must pick the missing square on the pattern from 5 response choices, and the task is discontinued after the participant makes 5 consecutive incorrect answers. Scoring is based on the number of correct responses.

### **Short Penn Continuous Performance Test**

Sustained attention was assessed using the Short Penn Continuous Performance Test (SPCPT).<sup>18</sup> Participants are presented with vertical and horizontal lines flashed on the computer screen for 300 ms in 2 blocks of 90 stimuli. In 1 block, they are asked to respond when the lines form a number. In the other block, they are asked to respond when the lines form a letter. Some trials present a distractor, in which the lines form a shape that is neither a letter nor a number. The total score is based on the number of correct responses and reaction time.

### **Dimensional Change Card Sort Test**

The set-shifting component of executive function was assessed using the Dimensional Change Card Sort Test from the NIH Toolbox.<sup>16</sup> In each trial, participants must match a visual target stimulus to 1 of 2 stimuli based on shape or colour. The dimension being matched is sometimes switched, requiring cognitive flexibility to change sorting rules and match the correct stimulus. Scoring is based on a combination of accuracy and reaction time.

### **Flanker Inhibitory Control and Attention Test**

The ability to inhibit attention to irrelevant stimuli (i.e., component of executive function) was assessed using the Flanker Inhibitory Control and Attention Test from the NIH Toolbox.<sup>16</sup> In each trial, the participant must indicate the direction that the target arrow is pointing, while ignoring the direction of the distractor arrows (flankers). The flanker arrows face the same direction as the target arrow in congruent trials, and in the opposite direction to the target arrow in incongruent trials. Scores are based on accuracy and reaction time, and converted to an age-adjusted score.

### **Pattern Comparison Processing Speed Test**

Processing speed was assessed using the Pattern Comparison Processing Speed Test from the NIH Toolbox.<sup>16</sup> This test requires participants to indicate whether 2 adjacent pictures are the same or different. Scoring is based on the number of items correct within a 90-second time limit, and the raw score is converted to an age-adjusted score.

### **Delay discounting task**

Immediate reward preference — or devaluing of delayed rewards — was assessed using an adjusting-amount monetary choice task. In this paradigm, each trial asks participants to indicate whether they would rather receive a smaller immediate reward (e.g., \$100 today) or a larger delayed reward (e.g., \$200 in 3 months). The delay in time to receipt of the later reward was kept fixed, and the reward amounts were titrated based on participants' choices until points of indifference were determined. The variable used to measure how steeply participants discounted delayed rewards was area under the curve (AUC), a valid and reliable index of immediate reward preference.<sup>19</sup> Given the strong correlation between the 2 magnitudes ( $r = 0.676$ ,  $p < 0.001$ ), we averaged the AUC variables for smaller (i.e., \$200) and larger (i.e., \$40 000) delayed reward conditions into a single composite variable.

### **Penn Word Memory Test**

Verbal episodic memory was assessed using the Penn Word Memory Test, a forced-choice recognition task.<sup>20</sup> In the encoding phase, participants are shown a series of 20 target words and asked to remember them. The delayed recognition trials require participants to identify from a list of 40 words (20 of which are distractor items) the words that were in the original list. They can respond by choosing from "definitely no," "probably no," "probably yes" and "definitely yes." Performance measures are the number of correctly identified target words and the reaction time for true positive responses.

### **List Sorting Working Memory Test**

Working memory was assessed using the List Sorting Working Memory Test from the NIH Toolbox,<sup>16</sup> in which participants are presented with visual (pictures) and oral (spoken names) information about various foods and animals. In the 1-list condition, participants are presented with and asked to order animals or foods from smallest to largest. In the 2-list condition, participants are presented with both animal and food lists and asked to order each list by increasing size. The number of list items increases with subsequent trials, and the task is discontinued after 2 subsequent incorrect trials. Raw scores are the sum of the total correct items, which is converted to an age-adjusted score.

### **9-Hole Pegboard Dexterity Test**

Psychomotor dexterity was measured using the 9-Hole Pegboard Dexterity Test from the NIH Toolbox.<sup>21</sup> Participants are required to accurately place and remove 9 plastic pegs into a pegboard as quickly as possible. This procedure is performed for 1 practice and 1 timed trial for each hand, and raw scores are time to completion recorded separately for each hand.

### *Statistical analysis*

First, we examined the data for missingness, finding  $< 1.0\%$  missing for all variables of interest. We retained only participants with complete data. Next, we winsorized outlying values ( $Z$ -scores  $> 3.29$ ) for dependent variables to 1 unit greater

than the closest nonoutlying value.<sup>22</sup> A total of 26 cases had any outlying values (Penn Word Memory Test = 0.26%; Dimensional Change Card Sort Test = 0.53%; Flanker Inhibitory Control and Attention Test = 0.26%; SPCPT = 1.25%). Distribution normality was examined, and scores on the Penn Word Memory Test, Flanker Inhibitory Control and Attention Test, and delay discounting AUC were all transformed using square-root transformations; the SPCPT and Raven's Progressive Matrices were transformed using logarithmic transformations.

To address potential confounders, we included the following demographic, substance use and HCP design covariates: age, sex, income, years of education, tobacco use, alcohol use, dizygotic twin status and monozygotic twin status. With regard to twin status, the HCP design includes a number of twin dyads, which was addressed using the approach of Pagliaccio and colleagues.<sup>23</sup> The primary analyses comprised hierarchical linear regression models to examine cannabis variables (and covariates) in relation to neurocognitive task performance. Specifically, to reduce the likelihood of type I errors, covariates were entered in a first step and cannabis involvement variables were then entered collectively in a second step (effectively acting as an omnibus test). Individual tasks were then examined further if the cannabis variables collectively significantly improved the overall model ( $\Delta R^2$ ). We evaluated collinearity among independent variables using a variance inflation factor of  $> 2.50$  and a tolerance of  $< 0.20$  as criteria for detecting multicollinearity. Recognizing the relatively large number of tests being conducted, we used a type I error threshold of  $\alpha = 0.005$  for the primary analyses to reduce the likelihood of false-positive findings.<sup>24</sup> Because the study used an open-science data set, we did not conduct a priori power analyses. However, to inform power, we generated the minimum detectable effect for the HCP sample size. At a power of 0.80 and  $p < 0.005$  (the threshold used), the minimum detectable effect was  $f^2 = 0.016$  (partial  $R^2 = 0.014$ ). At a power of 0.99, the minimum detectable effect increased to  $f^2 = 0.03$  (partial  $R^2 = 0.031$ ). In standard magnitude conventions, an  $f^2$  of 0.02 is considered small, 0.15 is considered medium, and 0.35 is considered large, meaning that the cohort was well powered to detect associations of small magnitude or larger. Finally, we re-ran the primary analyses separately for male and female participants for exploratory purposes. All analyses were conducted in SPSS v. 25 (SPSS Inc.).

## Results

### Participants

Descriptive statistics for participants ( $n = 1121$ ) are shown in Table 1.

### Preliminary analyses

Correlations among the candidate covariates and cannabis use variables revealed significant associations (Appendix 1, Table S1, available at [jpn.ca/180115-a1](http://jpn.ca/180115-a1)) that supported their incorporation into the primary analyses. Zero-order

correlations among the cannabis variables and neurocognitive measures are reported in Table 2, revealing numerous significant associations in the absence of adjustment for potential confounders. Lifetime cannabis use and age at first use were very strongly correlated ( $r = 0.80$ ,  $p < 0.001$ ) and were not examined in joint models to avoid collinearity. Lifetime cannabis use was used as the primary variable, and age at first use is reported in Appendix 1.

### Primary analyses

In the hierarchical regressions, after controlling for covariates, cannabis involvement explained significantly more variance in performance on Raven's Progressive Matrices, the Picture Sequence Memory Test and the Pattern Comparison Processing Speed Test (Table 3). Individual regressions are shown in Table 4. Inspection of the coefficients revealed that the significant omnibus models were driven largely by significant associations between a positive drug screen for THC and task performance. Specifically, a positive THC drug screen was associated with significantly fewer correct responses for the Picture Sequence Memory Test and lower age-adjusted scaled scores for the Pattern Comparison Processing Speed Test. In addition, meeting diagnostic criteria for CUD was associated with significantly fewer correct responses on Raven's Progressive Matrices.

Hierarchical regressions replacing lifetime cannabis exposure with age at first cannabis use in the cannabis involvement block (to avoid collinearity) did not change any models substantively (Appendix 1, Table S2), and age at first use was not a significant predictor in the examination of individual coefficients (Appendix 1, Table S3).

**Table 1: Sample characteristics ( $n = 1121$ )**

Characteristic	No. (%) <sup>*</sup>
Mean age $\pm$ SD, yr	28.8 $\pm$ 3.7
Female, %	53.4
Median income per yr, \$	40 000–49 000
Mean education $\pm$ SD, yr	14.9 $\pm$ 1.8
Tobacco use	237 (21.1)
Median frequency of alcohol use, no. d/mo	1–3
Lifetime cannabis use	
Never used	482 (43.0)
1–10 times used	317 (28.3)
11–100 times used	139 (12.4)
101–999 times used	76 (6.8)
1000+ times used	107 (9.5)
CUD+	109 (9.7)
THC+ urine drug screen	135 (12.0)
Cannabis age at first use	
$> 21$ yr	124 (11.1)
18–20 yr	203 (18.1)
15–17 yr	233 (20.8)
$< 14$ yr	79 (7.0)

CUD = cannabis use disorder; SD = standard deviation; THC = tetrahydrocannabinol.  
<sup>\*</sup>Unless indicated otherwise.

### Sex-specific associations

Separate results for men and women are shown in Table 5 and generally reproduced the primary findings. Sex-stratified individual regressions are shown in Appendix 1, Table S4. Effect sizes were similar for Raven's Progressive Matrices and the Pattern Comparison Processing Speed Test, and nominal statistical significance was present for both sexes, although it was marginal for men for the Pattern Comparison Processing Speed Test. Weaker statistical significance in general was not surprising, given that we had approximately half the sample size for sex-specific associations. An exception to the parallel findings was a noticeably larger effect for the Picture Sequence Memory Test for men than for women.

### Discussion

The primary aim of this study was to examine the association between cannabis involvement and neurocognitive task performance in a large sample of generally healthy young adults. Overall, recent use of cannabis, as indicated by the presence of THC, was the strongest determinant of neurocognitive task performance. The presence of THC in urine was inversely related to performance on the Picture Sequence Memory Test and the Pattern Comparison Processing Speed Test, such that participants who screened positive for THC tended to exhibit worse episodic memory and slower processing speed than those who screened negative. Interestingly, the only neurocognitive domain significantly predicted by CUD status was fluid intelligence, as measured by Raven's Progressive Matrices.

The finding that THC presence predicts poorer performance on an episodic memory task is in line with previous studies finding a similar association between acute THC administration or recent cannabis use and episodic memory.<sup>25–27</sup> Diminished processing speed as a function of recent THC exposure is also consistent with the literature. Several studies have found that, compared with placebo controls, participants administered THC required more time to make decisions<sup>28,29</sup> and performed slower on direct measures of processing speed.<sup>30</sup> A recently published meta-analysis of 69 studies examining the impact of cannabis use in young adults found no difference in effect size based on age of first use or on the mean age of the sample.<sup>31</sup> However, the authors found that 72 hours of abstinence substantially reduced the observed cognitive deficits associated with cannabis use, consistent with the present findings of recent use having stronger associations with cognitive performance than age at onset, lifetime use and severity of use. It is therefore likely that certain cognitive abilities are both acutely impacted by THC during intoxication and subsequently affected while residual levels of THC are present in the body. In other words, cannabis effects on these aspects of cognition meaningfully extend beyond episodes of intoxication. Importantly, these observed deficits are not generalized across cognition and are presumably reversed as THC is eliminated from the body via prolonged cannabis abstinence.

Table 2: Zero-order correlation matrix between cannabis involvement variables and neuropsychological task performance

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13
1. THC+ urine drug screen	—												
2. CUD+	0.271**	—											
3. Cannabis age of first use	0.329**	0.409**	—										
4. Lifetime cannabis use	0.502**	0.556**	0.800**	—									
5. Penn Word Memory Test	0.117**	−0.040	−0.061*	−0.063	—								
6. Flanker Inhibitory Control and Attention Test	0.111**	0.006	0.037	0.058	−0.079	—							
7. Dimensional Change Card Sort Test	−0.087**	0.018	0.005	0.017	0.150**	−0.512**	—						
8. Short Penn Continuous Performance Test	−0.069	0.035	−0.009	0.014	0.111**	−0.119**	0.152**	—					
9. Raven's Progressive Matrices	0.145**	−0.041	0.074	0.050	−0.218**	0.137**	−0.195**	−0.188**	—				
10. Delay discounting task	−0.137**	−0.016	−0.056	−0.056	0.114**	−0.056	0.058	0.064	−0.215**	—			
11. Picture Sequence Memory Test	−0.165**	−0.028	−0.026	−0.061	0.242**	−0.150**	0.214**	0.160**	−0.293**	0.081*	—		
12. Pattern Comparison Processing Speed Test	−0.144**	0.010	−0.043	−0.041	0.143**	−0.379**	0.425**	0.123**	−0.157**	0.047	0.204**	—	
13. List Sorting Working Memory Test	−0.140**	−0.014	−0.038	−0.043	0.158**	−0.138**	0.209**	0.145**	−0.341**	0.125**	0.345**	0.182**	—
14. 9-Hole Pegboard Dexterity Test	−0.174**	−0.073	−0.071	−0.127**	0.107**	−0.139**	0.165**	0.057	−0.154**	0.119**	0.194**	0.192**	0.108**

CUD = cannabis use disorder; THC = tetrahydrocannabinol.

\*Correlation is significant at the 0.005 level (2-tailed).

\*\*Correlation is significant at the 0.001 level (2-tailed).

**Table 3: Hierarchical regressions comprising a covariate model followed by cannabis involvement variables (urinary tetrahydrocannabinol, lifetime cannabis use, cannabis use disorder) in relation to neuropsychological performance**

Neuropsychological variable	Covariate model R <sup>2</sup>	p value	Cannabis involvement $\Delta$ R <sup>2</sup>	p value
Penn Word Memory Test	0.050	< 0.001*	0.003	0.392
Flanker Inhibitory Control and Attention Test	0.024	< 0.001*	0.010	0.011
Dimensional Change Card Sort Test	0.032	< 0.001*	0.003	0.337
Short Penn Continuous Performance Test	0.049	< 0.001*	0.008	0.029
Raven's Progressive Matrices	0.142	< 0.001*	0.010	0.003*
Delay discounting task	0.063	< 0.001*	0.003	0.272
Picture Sequence Memory Test	0.070	< 0.001*	0.010	0.004*
Pattern Comparison Processing Speed Test	0.026	< 0.001*	0.015	0.001*
List Sorting Working Memory Test	0.067	< 0.001*	0.006	0.060
9-Hole Pegboard Dexterity Test	0.104	< 0.001*	0.005	0.097

\*Significant at the  $p < 0.005$  level.**Table 4: Individual hierarchical regressions of covariates and cannabis involvement variables in relation to neuropsychological performance for models significant at the  $p < 0.005$  level**

Model	Variable	Raven's Progressive Matrices		Picture Sequence Memory Test		Pattern Comparison Processing Speed Test	
		$\beta$	p value	$\beta$	p value	$\beta$	p value
Covariate model	Sex	0.147	<0.001*	0.148	<0.001*	0.019	0.550
	Age	0.083	0.005*	-0.037	0.226	-0.042	0.177
	Income	-0.064	0.041	0.070	0.032	0.060	0.069
	Education	-0.250	<0.001*	0.172	<0.001*	0.072	0.033
	Tobacco use	0.094	0.002*	0.019	0.557	-0.002	0.960
	Alcohol use	0.032	0.254	-0.016	0.609	-0.053	0.098
	Dizygotic twin status	-0.011	0.707	0.034	0.253	0.075	0.013
	Monozygotic twin status	-0.013	0.452	-0.002	0.944	0.053	0.081
Cannabis involvement	THC+ urine drug screen	0.057	0.089	-0.121	<0.001*	-0.132	<0.001*
	Lifetime cannabis use	0.046	0.233	0.028	0.486	-0.007	0.873
	CUD+	-0.104	0.002*	0.033	0.342	0.055	0.119

CUD = cannabis use disorder; THC = tetrahydrocannabinol.

\*Significant at the  $p < 0.005$  level.

With regard to the finding for Raven's Progressive Matrices, lower fluid intelligence for those who met the criteria for CUD is also compatible with the previous literature. A longitudinal co-twin study by Meier and colleagues<sup>11</sup> tested the IQ of twins at ages 5, 12 and 18 years and found that adolescents who met the criteria for CUD had a lower IQ in childhood than adolescents without cannabis dependence and that these differences predated the age at first cannabis use. Furthermore, they found no association between CUD status and changes in IQ over the developmental period, which supports the idea that lower IQ predates the onset of cannabis use itself. Differences in intelligence as a function of CUD status in our sample may also have predated cannabis involvement, but without repeated measures of IQ over the developmental period, this is speculation.

Interestingly, cannabis involvement was not associated with performance on measures of impulsivity, processes that have generally been associated with substance misuse and other conditions associated with deficits in self-regulation.<sup>32-35</sup>

Importantly, it is increasingly recognized that impulsivity is a multidimensional construct;<sup>36-38</sup> some evidence suggests 3 broad domains, 2 of which are behavioural inhibition (SPCPT and Flanker Inhibitory Control and Attention Test in this study) and impulsive delay discounting.<sup>39</sup> Cannabis involvement failed to predict performance on any of these tasks. However, the literature is more inconsistent for whether cannabis users exhibit deficits in inhibition<sup>6</sup> and monetary delay discounting.<sup>39,40</sup> In other words, these findings are compatible with a broader literature indicating that cannabis may be systematically different from other substances in these domains. Finally, it is worth noting that although self-regulation is a core feature of substance misuse, it is by no means the only one. Other core features include persistent negative emotionality and dysregulated incentive salience processing,<sup>41</sup> neither of which fell within the purview of the current study.

A number of nuances bear on the implications of these findings. Although the associations observed were statistically significant, they were small in magnitude in terms of

**Table 5: Sex-stratified hierarchical regressions comprising the covariate model followed by the cannabis involvement variables (i.e., urinary tetrahydrocannabinol, lifetime cannabis use, cannabis use disorder) in relation to neuropsychological indicators.**

Neuropsychological measure	Male covariate model, $R^2$	Male covariate model, $p$	Male cannabis involvement, $\Delta R^2$	Male cannabis involvement, $p$	Female covariate model, $R^2$	Female covariate model, $p$	Female cannabis involvement, $\Delta R^2$	Female cannabis involvement, $p$
Penn Word Memory Test	0.035	0.011	0.019	0.018	0.069	<0.001	0.006	0.271
Flanker Inhibitory Control and Attention Test	0.036	0.008	0.013	0.070	0.032	0.008	0.006	0.317
Dimensional Change Card Sort Test	0.050	<0.001	0.004	0.533	0.046	<0.001	0.002	0.763
Short Penn Continuous Performance Test	0.062	<0.001	0.011	0.114	0.052	<0.001	0.008	0.157
Raven's Progressive Matrices	0.098	<0.001	0.016	0.027	0.178	<0.001	0.017	0.007
Delay discounting task	0.070	<0.001	0.009	0.160	0.080	<0.001	0.004	0.460
Picture Sequence Memory Test	0.036	0.009	0.026	0.003	0.081	<0.001	0.006	0.280
Pattern Comparison Processing Speed Test	0.047	0.001	0.014	0.050	0.049	<0.001	0.019	0.007
List Sorting Working Memory Test	0.067	<0.001	0.010	0.146	0.080	<0.001	0.005	0.319
9-Hole Pegboard Dexterity Test	0.055	<0.001	0.016	0.029	0.066	<0.001	0.002	0.794

effect size. Given the large sample size, it was possible to use an extensive list of covariates and detect subtle differences in neuropsychological performance; we did detect modest differences. In addition, a common theme was that the neuropsychological tasks significantly predicted by cannabis involvement were nonverbal, falling in the visuospatial domain of cognition. Furthermore, the measures involving simple visuospatial processing (i.e., Pattern Comparison Processing Speed Test, Picture Sequence Memory Test) were the outcomes significantly predicted by the presence of THC. As such, these effects may be less readily detectable experientially (as opposed to deficits in explicit declarative cognitive domains), obscuring them from the individual. In this context, even small deficits in visuospatial cognition may add significant risk in high-stakes, safety-sensitive occupational settings (e.g., pilot, crane operator, police officer, soldier), especially if the person is unaware of subtle changes in performance.

With regard to sex, exploratory analyses generally did not suggest meaningful differences, with 1 exception. Men exhibited notably greater impairment in processing speed than women, perhaps suggesting that men may be more sensitive to residual effects in that domain. On the other hand, men also exhibited greater cannabis involvement, which may have increased the capacity to detect effects. In general, because this is the first instance of this finding (to our knowledge), it should be interpreted cautiously and warrants further investigation in future studies.

### Limitations

These results should be interpreted with consideration of a number of limitations. The data do not provide fine-grained measures of the quantity and frequency of cannabis use, peak level of use (and recency of peak use), type of cannabis or method of administration, all of which could have provided a greater understanding of the links between cannabis and cognition. Similarly, CUD diagnosis reflects lifetime status, not current status, which would substantially add resolution. However, the HCP study was principally designed to understand human brain connectomics, not consequences of cannabis use per se, so the relatively coarse measurement of cannabis involvement is not surprising. A related consideration is that the age range was restricted to adults aged 22–36 years, again to optimize the overall HCP design, and may not capture the neurotoxic effects of prolonged heavy use over many years. On the other hand, a major strength of the present study is its large sample and extensive battery of neuropsychological assessments. As such, analyses were well powered to detect even small differences, and diverse aspects of cognitive performance were tapped. Less a limitation than a consideration, the HCP cohort represents a relatively healthy population when it comes to cannabis use, with greater representation of lower-level use than very heavy use. However, a critical question when it comes to cannabis and cognition is whether effects pertain to low-level use that reflects common consumption patterns, and this study addresses this question, suggesting no effects in most domains.

## Conclusion

The present findings provide evidence for significant links between recent cannabis use and specific visuospatial neurocognitive abilities, and an association between CUD and overall fluid intelligence, but not other areas. No links to age of first use were apparent. Although the effect sizes were of small magnitude and most domains were unaffected, this study nonetheless documents potential risks of recent cannabis use to people in professions that rely on optimum cognitive performance.

**Acknowledgements:** The data used in this project are from the Human Connectome Project, WU-Minn Consortium (principal investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 National Institutes of Health (NIH) institutes and centres that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University in St. Louis. The authors are deeply appreciative of the Human Connectome Project for open access to its data. In addition, the work was partially supported by the Peter Boris Chair in Addictions Research (J. MacKillop) and the Gary Sperduto Endowed Professorship in Clinical Psychology (L. Sweet). No funding sources were involved in study design or collection, or in the analysis and interpretation of the data. These findings do not reflect the official position of the National Institutes of Health.

**Affiliations:** From the Peter Boris Centre for Addictions Research, McMaster University/St. Joseph's Healthcare Hamilton, Hamilton, Ont., Canada (Petker, Amlung, MacKillop); the Department of Psychology, Neuroscience, and Behaviour, McMaster University, Hamilton, Ont., Canada (Petker, Amlung, MacKillop); the Addiction Medicine Service, Homewood Health Centre, Guelph, Ont., Canada (Petker, Owens); the Department of Psychology, University of Georgia, Athens, GA, USA (Sweet, MacKillop); the Michael G. DeGroote Centre for Medicinal Cannabis Research, McMaster University/St. Joseph's Healthcare Hamilton, Hamilton, Ont., Canada (Amlung, MacKillop); the Department of Human Development and Family Science, University of Georgia, Athens, GA, USA (Oshri); the Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, RI, USA (Sweet); and the Homewood Research Institute, Guelph, Ont., Canada (MacKillop).

**Competing interests:** J. MacKillop is a principal in BEAM Diagnostics, Inc. No other competing interests declared.

**Contributors:** T. Petker and J. MacKillop designed the study. The data were provided by the Washington University–University of Minnesota Consortium Human Connectome Project. T. Petker analyzed the data and all authors interpreted the findings. T. Petker drafted the article, which was edited and augmented by the other authors. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

## References

- World Health Organization. Cannabis. Geneva: World Health Organization; 2010.
- Rotermann M, Macdonald R. Analysis of trends in the prevalence of cannabis use in Canada, 1985 to 2015. *Health Rep* 2018;29:10-20.
- Intiaz S, Shield KD, Roerecke M, et al. The burden of disease attributable to cannabis use in Canada in 2012. *Addiction* 2016;111:653-62.
- Volkow ND, Swanson JM, Evins AE, et al. Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. *JAMA Psychiatry* 2016;73:292.
- Broyd SJ, Van Hell HH, Beale C, et al. Acute and chronic effects of cannabinoids on human cognition: a systematic review. *Biol Psychiatry* 2016;79:557-67.
- Ganzer F, Bröning S, Kraft S, et al. Weighing the evidence: a systematic review on long-term neurocognitive effects of cannabis use in abstinent adolescents and adults. *Neuropsychol Rev* 2016;26:186-222.
- Prashad S, Filbey FM. Cognitive motor deficits in cannabis users. *Curr Opin Behav Sci* 2017;13:1-7.
- Pope HG, Gruber AJ, Hudson JL, et al. Early-onset cannabis use and cognitive deficits: what is the nature of the association? *Drug Alcohol Depend* 2003;69:303-10.
- Gruber SA, Sagar KA, Dahlgren MK, et al. Age of onset of marijuana use and executive function. *Psychol Addict Behav* 2012;26:496-506.
- Solowij N, Jones KA, Rozman ME, et al. Verbal learning and memory in adolescent cannabis users, alcohol users and non-users. *Psychopharmacology (Berl)* 2011;216:131-44.
- Meier MH, Caspi A, Danese A, et al. Associations between adolescent cannabis use and neuropsychological decline: a longitudinal co-twin control study. *Addiction* 2018;113:257-65.
- Mokrysz C, Landy R, Gage SH, et al. Are IQ and educational outcomes in teenagers related to their cannabis use? A prospective cohort study. *J Psychopharmacol* 2016;30:159-68.
- Van Essen DC, Smith SM, Barch DM, et al. The WU-Minn Human Connectome Project: an overview. *Neuroimage* 2013;80:62-79.
- Cooper ZD, Craft RM. Sex-dependent effects of cannabis and cannabinoids: a translational perspective. *Neuropsychopharmacology* 2018;43:34-51.
- Bucholz KK, Cadoret R, Cloninger CR, et al. A new, semi-structured psychiatric interview for use in genetic linkage studies: a report on the reliability of the SSAGA. *J Stud Alcohol* 1994;55:149-58.
- Weintraub S, Dikmen SS, Heaton RK, et al. Cognition assessment using the NIH Toolbox. *Neurology* 2013;80:554-64.
- Bilker WB, Hansen JA, Brensinger CM, et al. Development of abbreviated nine-item forms of the Raven's Standard Progressive Matrices Test. *Assessment* 2012;19:354-69.
- Kurtz MM, Ragland JD, Bilker W, et al. Comparison of the continuous performance test with and without working memory demands in healthy controls and patients with schizophrenia. *Schizophr Res* 2001;48:307-16.
- Myerson J, Green L, Warusawitharana M. Area under the curve as a measure of discounting. *J Exp Anal Behav* 2001;76:235-43.
- Gur RC, Ragland JD, Moberg PJ, et al. Computerized neurocognitive scanning: I. Methodology and validation in healthy people. *Neuropsychopharmacology* 2001;25:766-76.
- Reuben DB, Magasi S, McCreath HE, et al. Motor assessment using the NIH Toolbox. *Neurology* 2013;80:565-75.
- Tabachnick BG, Fidell LS. *Using multivariate statistics*, 4th ed. New York: Pearson; 2001.
- Pagliaccio D, Barch DM, Bogdan R, et al. Shared predisposition in the association between cannabis use and subcortical brain structure. *JAMA psychiatry* 2015;72:994-1001.
- Benjamin DJ, Berger JO, Johannesson M, et al. Redefine statistical significance. *Nat Hum Behav Nature Publishing Group* 2018;2:6-10.
- Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. *J Addict Med* 2011;5:1-8.
- Gonzalez R, Schuster RM, Mermelstein RJ, et al. Performance of young adult cannabis users on neurocognitive measures of impulsive behavior and their relationship to symptoms of cannabis use disorders. *J Clin Exp Neuropsychol* 2012;34:962-76.

27. Ramaekers JG, Kauert G, Theunissen EL, et al. Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. *J Psychopharmacol* 2009;23:266-77.
28. Ramaekers JG, Kauert G, Van Ruitenbeek P, et al. High-potency marijuana impairs executive function and inhibitory motor control. *Neuropsychopharmacology* 2006;31:2296-303.
29. Vadhan NP, Hart CL, Van Gorp WG, et al. Acute effects of smoked marijuana on decision making, as assessed by a modified gambling task, in experienced marijuana users. *J Clin Exp Neuropsychol* 2007;29:357-64.
30. Fried PA, Watkinson B, Gray R. Neurocognitive consequences of marijuana—a comparison with pre-drug performance. *Neurotoxicol Teratol* 2005;27:231-9.
31. Scott JC, Slomiak ST, Jones JD, et al. Association of cannabis with cognitive functioning in adolescents and young adults. *JAMA Psychiatry* 2018;75:585-95.
32. Amlung M, Vedelago L, Acker J, et al. Steep delay discounting and addictive behavior: a meta-analysis of continuous associations. *Addiction* 2017;112:51-62.
33. MacKillop J, Amlung MT, Few LR, et al. Delayed reward discounting and addictive behavior: a meta-analysis. *Psychopharmacology* 2011;216:305-21.
34. Jackson JNS, Mackillop J. Attention-deficit/hyperactivity disorder and monetary delay discounting: a meta-analysis of case-control studies. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2016;1:316-25.
35. Amlung M, Petker T, Jackson J, et al. Steep discounting of delayed monetary and food rewards in obesity: a meta-analysis. *Psychol Med* 2016;46:2423-34.
36. Jentsch JD, Ashenhurst JR, Cervantes MC, et al. Dissecting impulsivity and its relationships to drug addictions. *Ann N Y Acad Sci* 2014;1327:1-26.
37. Kozak K, Lucatch AM, Lowe DJE, et al. The neurobiology of impulsivity and substance use disorders: implications for treatment. *Ann N Y Acad Sci* 2018 October 5 [Epub ahead of print]. doi: 10.1111/nyas.13977.
38. MacKillop J, Weafer JC, Gray J, et al. The latent structure of impulsivity: impulsive choice, impulsive action, and impulsive personality traits. *Psychopharmacology (Berl)* 2016;233:3361-70.
39. Strickland JC, Lile JA, Stoops WW. Unique prediction of cannabis use severity and behaviors by delay discounting and behavioral economic demand. *Behav Processes* 2017;140:33-40.
40. Johnson MW, Bickel WK, Baker F, et al. Delay discounting in current and former marijuana-dependent individuals. *Exp Clin Psychopharmacol* 2010;2010:99-107.
41. Kwako LE, Momenan R, Litten RZ, et al. Addictions neuroclinical assessment: a neuroscience-based framework for addictive disorders. *Biol Psychiatry* 2016;80:179-89.

# Journal of Psychiatry & Neuroscience

## Call for submissions

Have expertise treating patients with psychiatric disorders? Share it with clinicians in a Psychopharmacology for the Clinician column. Columns are 650 words and include a clinical vignette showcasing a topic of interest. Cases should have a level of complexity or novelty that will help clinicians make treatment decisions in situations that are not routine, or where new evidence is available but not widely known.

## Why write for *JPN*?

- *JPN* is the highest ranking open access journal in biological psychiatry
- Psychopharmacology for the Clinician columns are the most downloaded feature of *JPN* and archives are available indefinitely on [jpn.ca](http://jpn.ca) and in PubMed Central

20170047

Submit columns online at <https://mc.manuscriptcentral.com/jpn>.  
View previous columns at <https://jpn.ca/psychopharmacology-for-the-clinician/>